325 EFFECT OF HYPER- AND HYPOTHYROIDISM ON SERUM GROWTH HORMONE (rGH) IN THE DEVELOPING RAT.

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Brain and somatic growth are retarded by both experimental hyper- and hypothyroidism in the developing rat. Because of increasing use of thyroid replacement therapy in the human neonate we studied the effects of abnormal thyroid states on rGH during the neonatal period.

Litters of newborn rat pups were injected daily from ages 0-19 days with thyroxine (T4), 0.4 μg/gram of body weight, while littermate controls were injected daily with saline. Other litters were rendered hypothyroid by injection of the mothers with 50 mg. propylthiouracil (PTU) daily from 18 days gestation via intragastric gavage. Controls received an equal volume of saline.

In both experimental groups, the developmental curve for rGH in controls as measured by radioimmunoassay fell from 120 ng/ml on day one to 10 ng/ml on day 19. Both thyroxine and PTU treated pups showed a consistent depression in rGH levels at each age of early development. The maximum deficit in T4 animals was 6% of control at day 18, and in PTU animals, was 14% of control at day 15. Individual data points for treated and control animals were log transformed, following which the developmental profiles were analyzed by a one way analysis of covariance. Both hyper- and hypothyroid pups showed a statistically significant deficiency of rGH throughout early development. The early suppression in both conditions suggests the necessity for careful titration of thyroid replacement therapy in human congenital hypothyroidism.

326 EFFECTS OF THYROID HORMONE THERAPY IN CONGENITAL HYPOTHYROIDISM (CH).

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Among 15 infants with CH, 6 were identified in our screening program with an elevated cord TSH ($>$ 100 μU/ml) and low T_4 ($<$ 5 μg/dl), and placed on thyroid hormone therapy within the first month of life. Within 4 weeks of therapy their serum TSH was suppressed below 12 μU/ml either by treatment with T_4 alone or T_3 and T_4 combination therapy. An additional 9 infants not involved in a screening program were identified by clinical symptoms and referred for evaluation. Three infants were initially treated with 25 μg qd of T_3, and serum TSH was $<$ 12 μU/ml in all within 4 weeks. However, among 5 of 6 infants treated with T_4 alone, the TSH did not suppress below 12 μU/ml until $\geq$ 3 months of therapy.

During therapy in the 7 infants treated with T_4 alone, serial reverse T_3 (rT_3) determinations revealed peak concentrations (106 $\pm$ 13.8 ng/dl, mean $\pm$ SEM) simultaneous with the initial suppression of TSH to normal and significantly greater than the rT_3 levels just prior to suppression of TSH (66.7 $\pm$ 15 ng/dl, $p<.001$ by paired t test) and following TSH suppression (83.8 $\pm$ 16 ng/dl, $p<.05$). In summary, 1) T_4 alone is adequate therapy for CH identified early by screening programs, but is associated with delayed TSH suppression in infants diagnosed on the basis of clinical symptomatology alone. 2) The peak rT_3 levels associated with the initial TSH suppression suggest an increase in the monodeiodination of T_4 to rT_3, or decreased clearance of rT_3 which may indicate the development of intracellular euthyroidism.

327 HYPOGONADOTROPIC HYPOGONADISM (HHG) IN ACUTE INTERMITTENT PORPHYRIA (AIP),

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HHG in AIP has not been reported. A 20 yr. old male with AIP and inappropriate secretion of ADH was hyposmic, tall (178 cm), eunuchoid (U/L, 0.84), had a high-pitched voice, absent facial hair and Tanner 2-3 pubic hair. His testes were small (R, 8 ml; L, 10 ml). Karyotype was XY. Basal serum FSH, 5.5 mIU/ml; LH, 5.6 mIU/ml and T, 54 ng/dl were all low and PRL was normal. Mean nocturnal LH (6.5 $\pm$ 0.2 (SE) mIU/ml) was low and showed no periodic pulses. Mean nocturnal T (156 $\pm$ 13 ng/dl) was also low, with minimal fluctuations between 2200 h and 0300 h; however, between 0300 h and 0800 h two peaks of T occurred simultaneously with those of cortisol. The responses of LH to LHRH and TSH and PRL to TRH were normal. Nocturnal GH secretion was characterized by 3 peaks. Basal GH was normal and increased to 16 ng/ml during AITT and remained above 10 ng/ml between 60 and 150 minutes. Basal T, 252 ng/dl, increased to 2049 ng/dl after 4 days of im hCG (5000 units/d). Basal 24 h urine Δ amino levulinic acid (ALA), 18 mg and porphobilinogen (PBG), 68 mg, respectively, were high and did not change after 4 days of hCG (ALA, 25 mg/d; PBG, 51 mg/d). Three attacks of AIP occurred during 8 months prior to T therapy, but none occurred during 7 months of hCG or T therapy. Conclusions: 1) Hypothalamic dysfunction in AIP may cause HHG 2) hCG and T do not alter ALA and PBG excretion and may protect these patients from repeated attacks.

328 C-PEPTIDE EXCRETION DURING THERAPY OF DIABETIC KETOACIDOSIS.

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Measurement of serum and urine C-peptide (CPR) have been used to demonstrate residual insulin producing capacity in diabetes. The duration and dynamics of residual β-cell function have not been thoroughly investigated. Sequential measurement of serum and urine CPR were made during and after therapy for ketoacidosis in a 15 year old boy with JODM of 10 months duration. Serum CPR ranged from 0.3-0.6 ng/ml, approaching the lowest levels detectable by RIA. Urine C-peptide excretion increased over the 5 days of observation.

Day	C-peptide ng/mg creatinine	C-peptide ng/24o	$C_{creatinine}$ ml/min/1.73 M^2
1	0.67	843	128
2	0.88	3,895	123
3	3.57	5,238	60
4	5.39	9,463	101
5(1st 12 hrs.)	7.72	--	85

Urinary clearance and fractional excretion ($C_{C\text{-peptide}}/C_{creat.}$) of C-peptide also increased 6-10 fold.

Despite low serum CPR, these data are compatible with increased endogenous insulin production during therapy for ketoacidosis. Changes in renal blood flow or tubular disposition of C-peptide may have contributed to the progressive increase in urine C-peptide excretion.

329 11-DESOXYCORTICOSTERONE (DOC) AND 18-HYDROXY-DOC (18-OH-DOC) IN JUVENILE HYPERTENSION.

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Plasma DOC concentration and urinary excretion of tetrahydro-DOC (THDOC), free DOC and 18-OH-DOC, measured by specific radioimmunoassay, were similar in 7 children with essential hypertension and 4 patients with dexamethasone-suppressible hyperaldosteronism when compared with 5 normotensive controls (plasma DOC: 16.3±3.0 ng/dl, urinary excretion (μg/m^2/24h) of THDOC: 23.5±5.0 free DOC: 0.1±0.01, free 18-OH-DOC: 0.8±0.2). There was no correlation between DOC and 18-OH-DOC levels and plasma renin activity, severity or type of hypertension. During a continuous 5-day ACTH infusion (40 U/24h) urinary 18-OH-DOC increased 20-50 fold in all groups. Plasma DOC concentration and urinary THDOC excretion increased 20 fold, and urinary free DOC rose 20-50 fold in the control group and in the children with essential hypertension. The highest increase of THDOC (50 fold) and free DOC (100 fold) after ACTH was seen in the children with dexamethasone-suppressible hyperaldosteronism. However neither the observed salt retention nor the rise in blood pressure after ACTH stimulation were correlated with DOC or 18-OH-DOC in any of the groups. The rise in blood pressure after ACTH was independent of changes in salt and water balance. Conclusions: 1) DOC and 18-OH-DOC do not appear to play a major role in most cases of juvenile hypertension. 2) The marked rise of DOC and 18-OH-DOC may contribute to the rise in blood pressure with ACTH. 3) The blood pressure elevation after ACTH cannot be solely attributed to salt retention resulting from an increase in DOC secretion.

330 BIOACTIVE AND IMMUNOREACTIVE SERUM LH IN NORMAL PREPUBERTAL AND PUBERTAL BOYS.

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The testosterone (T) secretion of collagenase-dispersed rat interstitial cells exposed to gonadotropin provides a highly sensitive in vitro bioassay (RICT) for LH (Dufau et al, JCEM 39: 610, 1974). The serum levels of biologically active (B) LH and the relationship to immunoreactive (I) LH have been studied in 12 prepubertal (PRE) (age 2-17, $\bar{T}$=9.0 ng/dl) and 12 pubertal (PUB) (age 10-16, $\bar{T}$=164) normal males. Mean B-LH levels in PRE ($<$ 1mIU/ml, IRP-2-hMG) are significantly ($p<.001$) lower than in PUB (13.8±2.4 ($\bar{X}$±SE). B-LH was undetectable in all PRE and not separable by Tanner stages in PUB. I-LH levels, measured by double-antibody RIA, in PRE (3.6±1.0) are also lower ($p<.01$) than in PUB (9.3±1.5). B/I ratios in PRE (<0.6) are lower than in PUB (2.1±0.7). The B/I ratio in PRE is lower than in normal adult males (2.5±0.1) and closer to the levels reported in normal premenopausal women (1.2±0.1). The B/I ratio in PUB does not differ from that in adult males. In conclusion: (1) The RICT bioassay method for quantitating serum LH is applicable to studies in childhood; (2) RIA measurements of LH apparently overestimate true bioactive concentrations in subjects with minimal pituitary LH secretion; (3) The similarity of B/I ratio in PRE males to adult premenopausal women and in PUB to adult males suggests that sex steroids may modulate the biologic quality, as well as quantity, of pituitary LH secretion.